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FURANODITERPENE DERIVATIVES
[フラノジテルペン誘導体]

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Native Title : [フラノジテルペン誘導体]

English Title : Furanoditerpene derivatives

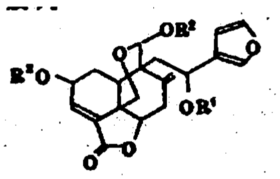
Specification

1. Title of the invention

Furanoditerpene derivatives

2. Scope of the patent claim

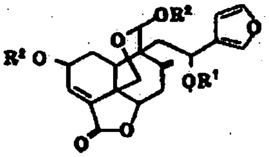
General formula



Furanoditerpene derivatives with (in the formula, R1 and R2 are identical or different and show a hydrogen atom(s) or lower aliphatic acyl group.)

3. Detailed explanation of the invention

This invention relates to the novel Furanoditerpene derivatives. In a greater detail, it relates to the novel Furanoditerpene derivatives with a general formula (in the formula, R1 and R2 are identical or different and show a hydrogen atom(s) or lower aliphatic acyl group.).



In the favorable compound expressed in the aforementioned general formula (I), R1 and R2 are identical or different and show hydrogen atoms, or show alkanoil group such as acetyl, propionyl, butyryl, and isobutyryl.

As to the favorable compounds obtained by this invention, the following can be listed: plaunol isolated from croton family plants later described (in the general formula (I), R1 and R2 both show hydrogen atom(s)); plaunol acetate (in the general formula (I), R1 shows acetyl group, and R2 shows hydrogen atom(s)); and plaunol triacetate synthesized by these compounds (in the general formula (I), R1 and R2 both show acetyl group).

Furanoditerpene derivatives (I) according to this invention is a useful compound as digestive system ulcer treatment drugs.

Inventors involved herein have been engaged in R&D of new drugs by isolating the plant ingredient with pharmacological activities for many years. The said inventors succeeded in isolating plaunol and plaunol acetate which are the novel Furanoditerpene derivatives contained in croton family plants, particularly Thailand produced plau-noi (croton sublyratus kurz, and Croton Columnaris Airy Shans, aka croton joufra Roxb), Plau-yai (Croton oblongifolius Roxb) and Plau-luat (Croton Huthcinsonianus Hossous), and in determining its chemical structures, furthermore, found out that Furanoditerpene derivatives shown in the general formula (I) is useful as the digestive system ulcer treatment drug and thus completed this invention.

Regarding the ulcer control activity of Furanoditerpene derivatives obtained here, the pharmacological testing shown below will clarify it.

Testing method

It was done according to the method of Shay et al (H. Shay, S. A Kumarow, S. S. Fels, D Meranze, M. Gryuentein, H. Siplet: Gastroenterology, vol 5, 43 (1945). Five rats per group at a time were used wherein male donryu type rats of the weight of 120 ~ 159g were after 48 hours of fasting. Under the ether anesthesia, the stomach was opened, and the boundary part of stomach [illeg] and duodenum are ligated and the stomach was closed again, and after 4 hours, by hitting the head part, rats are killed, and stomach is removed and gastric juice amount is measured. The specimen was administered into the abdominal cavity right after ligation.

Drug	Used amount Mg/kg	Gastric juice amount Ml/100g	Control rate %
Control	-	4.00	-
Plaunol	3	2.23	44
Plaunol	10	1.56	61
Plaunol acetate	3	1.91	52
Plaunol acetate	10	0.74	82
Plaunol triacetate	10	0.68	85
Plaunol triacetate isomer	10	1.37	69

Accordingly, the compounds with aforementioned general formula (I) is effective as ulcer treatment drug. AS the administration form for that purpose, in general, none-oral administration such as intravenous or hypodermal, or intramuscular injection, or oral administration such as tablets, or powders, capsule drugs etc are used. The usage amounts differ by ages, weights, administration methods, etc, however, usually, for an adult; it is 3mg ~ 1,000 mg a day.

According to the method of this invention, the compound with aforementioned general formula (I) can be obtained by the following method.

Method 1

Regarding the aforementioned general formula (I), in case R1 and R2 are both a hydrogen atom(s), that is, plaunol and R1 are acetyl group, and in case R2 is a hydrogen atom(s), that is, plaunol acetate is extracted by using solvent from croton family plant, and targeted compound is isolated from the extracted solution.

In the method of this invention, as the solvent used for extraction, the following can be used without particular limitation; water or organic solvent used to extract regular plant ingredient, for instance, alcohol types such as methanol, ethanol, isopropanol; halogenated hydrocarbon type such as dichlormethane, dichlorethan, chloroform, ester acetate type such as methyl acetate, ethyl acetate; lower alkyl keton type such as acetone, methyl ethyl keton; aromatic hydrocarbon type such as benzene, toluene etc.

In order to isolate aforementioned compound from this extraction solution, the regular plant neutral ingredient isolation method is applied, however, furthermore, it is advantageous to isolate combining with column chromatography.

That is, for instance, in order to remove the lipid from aforementioned extraction material, first, extraction solution or concentration are washed in hydrocarbon such as n-hexan, then, is extracted by water immiscible solvent such as benzene or ethyl ether acetate. Extraction solution is washed by alkaline bicarbonate water solution such as alkaline water, alkaline carbonate water solution such as sodium carbonate water solution or potassium carbonate water solution, thus, acid ingredients and water soluble ingredients are removed, and organic solvent layers are treated by drying agent such as sodium sulfuric anhydride, and solvent agent are distilled away from the solution. Extract thus obtained is washed by ether types such as ethyl ether and isopropyl ether, and ether soluble substances are distilled away. In order to isolate effective ingredients by ether insoluble fraction thus obtained, fillers such as silica gel, alumina and silica acid etc are used. And as development solvent, one type or two or more of organic solvent such as benzene, ethyl ester acetate, chloroform, acetone, and methanol etc are used a mixed solvent, and column chromatography is done. When solvent is distilled away from effluent, the targeted compound is obtained, however, if necessary, it could be refined by recrystallization method.

Method 2

In the aforementioned general formula (I), in case R1 and R2 are identical or different, and they are lower aliphatic acyl group, it can be obtained by having the compound obtained by the method 1 contact with acylation agent in the presence or non-presence of the solvent. As to acylation agent used, there is no particular limitation as long as they are used in general for acylation of a hydroxyl group and there is no impact on other part of compound, however, favorably, acid anhydride such as acetic anhydride, and propionic acid anhydride, and acidic halogenide such as croide acetate, promide acetate, buthyryl crolyd, isobutyryl chrolid are used. This reaction is done in the presence of an alkali to be favorable. Alkali to be used to be favorable are organic alkaline type such as triethyl amine, pyridine, picoline, lutidine, and alkaline metal hydroxide such as sodium hydroxide, potassium hydroxide, alkaline metal carbonate such as sodium carbonate, and potassium carbonate which is inorganic alkaline type, organic acid alkaline metallic salt such as sodium acetate, potassium acetate. As the solvent used, there is no limitation as long as it does not contribute to the reaction of this invention, however, to be favorable, water, ether type such as ethyl ether, tetrahydrofuran, dioxan; halogenated hydrocarbon such as methylene crolid, and chloroform; and aromatic hydrocarbon such as benzene, toluene; or hetero cycle alkali such as pyridine, and picoline. As to the reaction temperature, there is no limitation; it is done favorably in the vicinity up to zero degree of the room temperature.

The targeted compound obtained by above method can be refined, if necessary, by normal methods, for instance, column chromatography, or thin layered chromatography, furthermore, recrystallization method.

Next, the invention will be explained specifically using embodied cases; however, this invention is not limited to these.

Embodied case 1

Pulverized Thai plaunol 81.5 kg is extracted under heated reflux 3 times by acetone. Extracted liquid is combined and acetone is distilled away, thus, extraction 1647 g is obtained. Extraction is solved in 90% methanol 10 liter, and is washed by n- hexan 3 liters 3 times, and methanol is distilled away, concentration 1228 g is obtained. The concentration is added into 40 liters of benzene while being churned, and after churching violently for 30 minutes more, benzene layers is isolated from insoluble stuff. The concentration of 795 g obtained by distilling away the solvent from benzene layer is extracted by reflux using 2.5 liters of isopropyl ether and ether soluble substance is removed, thus, a fraction 400g which contains targeted compound is obtained and the fraction thus obtained is solved in chloroform, and is adsorbed into the column using 5.0 kg silica gel, and after eluting by 1% methanol containing chloroform, next, it is eluted by 2% methanol containing chloroform. Among the eluted fraction of 2% methanol containing chloroform, crystals are obtained by distilling away the solvent of the part which contains effective ingredient, these crystals are recrystalized by acetone-isopropyl ether mixed solution, and plaunol acetate of 12g is obtained.

Molecular formula: $C_{22}H_{24}O_8$

Melting point: 180 ~ 181 deg C

Angle of rotation: [alpha]D (acetone): -142 degree

Infrared absorption spectrum? cm^{-1} (nujol):

3380, 1750, 1720, 1675, 1635, 1505

1370, 1350, 1320, 1270, 1235, 1210

1190, 1160, 1135, 1090, 1070, 1040

1025, 1000, 980, 970, 905, 875

820, 760

Neuclea magnetic resonance spectrum, ? ppm (heavy acetone,

2.02 (3H, single line)

2.0 ~ 3.5 (7H, multiplet line)

4.75 (1H, four

5.07 (1H, double lines)

5.49 (1H, double lines)

5.71 (1H, single line)

5.75 (1H, multiplet line)

5.96 (1H, quoadlet line)

6.29 (1H, triplet line)

6.73 (1H, double lines)

7.34 (2H, multiplet line

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[1] Numbers in the margin indicate pagination in the foreign text.